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Low-Dose Continuous 5-Fluorouracil Combined with Leucovorin, *nab*-Paclitaxel, Oxaliplatin, and Bevacizumab for Patients with Advanced Pancreatic Cancer: A Retrospective Analysis

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Abstract

Background Continuous-infusion 5-fluorouracil (5FU) and calcium leucovorin plus *nab*-paclitaxel and oxaliplatin have been shown to be active in patients with pancreatic cancer. As a protracted low-dose infusion, 5FU is antiangiogenic, and has synergy with bevacizumab. As shown in the treatment of breast cancer, bevacizumab and *nab*-paclitaxel are also synergetic.

Objective In this paper we retrospectively analyze the survival of 65 patients with advanced pancreatic cancer who were treated with low-dose continuous (metronomic) chemotherapy given in conjunction with conventional anti-VEGF therapy.

Patients and Methods Since July of 2008, we have treated 65 patients with 5FU (180 mg/m²/day × 14 days) via an ambulatory pump. Calcium leucovorin (20 mg/m² IV), *nab*-paclitaxel (60 mg/m² IV as a 30-min infusion, and oxaliplatin (50 mg/m²) IV as a 60-min infusion were given on days 1, 8, and 15. Bevacizumab (5 mg/kg) IV over 30 min was administered on days 1 and 15. Cycles were repeated every 28–35 days. There were 42 women and 23 men, and the median age was 59 years. Forty-six patients had stage IV disease.

Results The median survival was 19 months, with 82% of patients surviving 12 months or longer. The overall response rate was 49%. There were 28 patients who had received prior treatment, 15 of whom responded to therapy. Fifty-two patients had elevated CA 19-9 prior to treatment. Of these, 21 patients had 90% or greater reduction in CA 19-9 levels. This cohort had an objective response rate of 71% and a median survival of 27 months. Thirty patients stopped treatment due to disease progression, and an additional 22 stopped because of toxicity. One patient died while on therapy.

Conclusions This non-gemcitabine-based regimen resulted in higher response rates and better survival than what is commonly observed with therapy given at conventional dosing schedules. Low-dose continuous (metronomic therapy) cytotoxic chemotherapy combined with antiangiogenic therapy is safe and effective.

Key Points

In our single institution experience treating 65 patients with advanced pancreatic cancer, one-year survival in our cohort was 82%, substantially higher than has been reported in clinical trials of other accepted therapies (35–48%).

The lower toxicity of our approach allowed for longer median duration of treatment compared to other accepted protocols.

A reduction in CA19-9 tumor marker levels by 90% or greater on therapy was associated with significantly longer median survival: 28 months versus 15 months.

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1 Introduction

Pancreatic ductal adenocarcinoma (PDA) is the third leading cause of cancer-related deaths in the United States. In 2015, an estimated 48,960 new cases were diagnosed, which resulted in 40,000 deaths [1]. Despite improved knowledge regarding the disease and the development of new targeted and immunologic therapies, along with the expanded availability of gene profiling, there has been little progress with respect to improved outcome. High mortality rates and short survival are explained by the lack of effective systemic therapies and the fact that most patients are diagnosed with late-stage disease [2].

Gemcitabine became the standard of care as first-line therapy for patients with metastatic disease, based on the phase III trial reported by Burris et al., which demonstrated a significant increase in clinical benefit rate (CBR, an endpoint that measured overall clinical improvement based on analgesic consumption, pain intensity, performance status, and weight change) and increased survival and time to disease progression when compared to 5-fluorouracil (5FU) [3]. More recently, Conroy et al. reported that a biweekly regimen of infusional 5FU, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) was superior to single-agent gemcitabine [4]. Patients who received FOLFIRINOX had median survival of 11.1 months, compared with 6.8 months observed for gemcitabine. Gemcitabine has been combined with a wide variety of chemotherapeutic drugs and targeted therapies, only to result in additional side effects and toxicity, without meaningful survival benefit [5–10]. The one exception is the addition of *nab*-paclitaxel to gemcitabine, as reported in October 2013 by Von Hoff et al., with median survival of 8.5 and 6.7 months for *nab*-paclitaxel plus gemcitabine and gemcitabine alone, respectively [11]. Apart from FOLFIRINOX and gemcitabine plus *nab*-paclitaxel, treatments remain largely ineffective.

Historically, regimens for pancreatic cancer have employed one, two, or three drugs at their maximum tolerated dose (MTD). Conventional MTD dosing is characterized by the administration of the highest possible dose, followed by a period of rest. In contrast, a low-dose metronomic (LDM) protocol is specifically designed to reduce dose-limiting side effects, is more patient-friendly, and has exhibited substantial rates of disease control in many adult solid tumors. This approach embraces the use of drugs administered at doses that are significantly lower than those considered standard, and usually given over prolonged periods of time, with fewer and shorter breaks [12]. Many examples of effective metronomic therapies have been reported in both pediatric and adult oncology [13–17].

In this paper we report the results of a retrospective analysis of 65 patients with advanced metastatic or locally advanced incurable pancreatic cancer. All patients received a protracted infusion of low-dose 5FU combined with *nab*-paclitaxel, calcium leucovorin, oxaliplatin, and bevacizumab. This

chemotherapeutic regimen was based on rational, scientific principles of cancer chemotherapy.

5FU is approved for the palliative management of patients with pancreatic cancer. Low-dose continuous 5FU infusion is more effective than bolus injections [18]. In a meta-analysis of 1219 cancer patients who received bolus versus infusional 5FU, tumor response was significantly higher in patients treated with continuous infusion versus bolus (22 vs. 14%), as was overall survival. Hematologic grade 3 or 4 toxicity was less common with infusional therapy. By combining oxaliplatin with infusional 5FU, Ducreux et al. observed higher response rates and significantly longer survival than with either infusional 5FU or oxaliplatin alone [19]. Adding irinotecan and oxaliplatin to infusional 5FU improved outcomes in the treatment of patients with pancreatic cancer compared to single-agent gemcitabine [4].

It has been shown that tumor cells that are resistant to chemotherapy at conventional doses will continue to be sensitive to low-dose therapy. This observation was first described by Browder and Klement [20, 21]. 5FU administered continuously at low doses possesses antiangiogenic properties [22, 23] which are potentiated when combined with bevacizumab, as seen in the treatment of colon, gastric, and pancreatic cancers [14, 24–28]. When infusional 5FU, leucovorin, and irinotecan (FOLFIRI) was combined with bevacizumab, the overall survival of 31.3 months compared favorably with that of 20.3 months reported with bolus 5FU, leucovorin, irinotecan, and bevacizumab, and to the 16-month survival reported with FOLFIRI alone [23]. Paclitaxel and docetaxel given weekly on a metronomic schedule are less toxic and more active than on the standard every-three-weeks dosing schedule [29, 30].

Inhibition of tumor angiogenesis by more effective dosing schedules and targeted inhibitors can enhance the therapeutic benefit. Elevated serum and tumor vascular endothelial growth factor (VEGF) levels correlate with poor prognosis in patients with pancreatic cancer, as do other plasma cytokines and pro-angiogenic factors that have been shown to predict drug resistance [31–33]. Bevacizumab has been shown to reverse the angiogenic effects of VEGF, and it can reduce tumor interstitial pressure, leading to enhanced drug delivery [34]. Continuous low-dose 5FU may be more effectively transported than bolus 5FU in an environment of high interstitial pressure [35]. In breast cancer, *nab*-paclitaxel has been shown to reach higher intratumoral concentrations and to improve survival compared with standard paclitaxel or docetaxel [36–38]. When *nab*-paclitaxel was combined with bevacizumab, a weekly dosing schedule resulted in higher progression-free survival (PFS) and overall survival (OS), with less toxicity, compared with dosing every 3 weeks or every 2 weeks [39, 40]. The inclusion of bevacizumab in this regimen may effectively prevent the effects of angiogenesis while enhancing the activity of both *nab*-paclitaxel and continuous-infusion 5FU.

2 Patients and Methods

2.1 Patients

All patients were treated at the University of California, Los Angeles (UCLA), in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines of the International Conference on Harmonisation, and were retrospectively selected for analysis. This study was approved by the UCLA Institutional Review Board (approval no. 18–000192), and the requirement for informed consent was waived for the entire study. Eligible patients included those with American Joint Committee on Cancer (AJCC) stage III locally advanced unresectable pancreatic adenocarcinoma or stage IV disease, histologically proven ductal or undifferentiated adenocarcinoma, and measurable or evaluable disease. Patients had Eastern Cooperative Oncology Group Performance Status of 0–2 and were > 18 years of age. All patients underwent baseline laboratory studies that included platelet count > 100,000/mm³, hemoglobin > 9.0 g/dL, absolute neutrophil count > 1500/mm³, ALT/AST < 2.5 times the upper limit of normal (ULN), total bilirubin < 1.5 times the ULN, and creatinine < 1.5 mg/dL. No patient initiated treatment until they were 2 weeks beyond surgical bypass procedure or had recovered from surgery. Patients who previously received prior chemotherapy were included. Patients were excluded if they had a concurrent second malignancy or known history of current or previous central nervous system (CNS) metastatic disease. Pregnant or nursing women were excluded.

2.2 Drug Dosing

Treatment consisted of 5FU 180 mg/m²/day as continuous infusion on days 1–15 via an ambulatory chemotherapy pump into a surgically placed central venous line (IV); nab-paclitaxel 60 mg/m² as a 30-min IV infusion, calcium leucovorin 20 mg/m² IV bolus injection, and oxaliplatin 50 mg/m² IV over 60 min on days 1, 8, and 15; and bevacizumab 5 mg/kg IV over 30 min every other week, on days 1 and 15. Cycles were repeated every 28–35 days. Treatment was continued until there was objective evidence of disease progression or unacceptable treatment-related toxicity, or at the patient's or physician's discretion.

2.3 Assessments

The primary objective was to quantify the percentage of patients alive at 1 year. Secondary endpoints included median survival, response rate, percentage reduction in carbohydrate antigen (CA)19-9 levels from baseline, and treatment safety.

All patients who completed at least one 15-day cycle of treatment were evaluated for treatment efficacy and safety.

Safety was assessed by the incidence of treatment-related adverse events (AE) according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0, and included grade 3/4 neutropenia with fever or grade 4 neutropenia lasting ≥ 3 days, any grade 4 hematologic toxicity, grade ≥ 3 thrombocytopenia with bleeding, or any grade 3/4 treatment-related non-hematologic toxicity, including vomiting, diarrhea, neuropathy, or stomatitis.

Response was assessed utilizing Response Evaluation Criteria In Solid Tumors (RECIST) guidelines. Computed tomography (CT) scans were compared against baseline imaging every 8–10 weeks. Serum CA19-9 levels were obtained each cycle. Overall survival was analyzed using the Kaplan–Meier method and a stratified log-rank test. Data were censored for patients who were still alive at the time of analysis. Survival was calculated from the day of initial therapy to the date of death or time of last follow-up.

3 Results

3.1 Cohort Characteristics

A total of 65 consecutive patients were treated and evaluated (Table 1). The median age of the patients was 59 years (range 26–80 years), and 42 patients were women. Nineteen patients had stage III disease; 46 had stage IV disease. Twenty-eight patients had undergone prior surgery for their disease. The median duration of treatment was 29 weeks (range 2–158 weeks). No patients were receiving chemotherapy at the time of assessment. Discontinuation of treatment occurred for the following reasons: all therapy was completed ($n = 3$), disease progression ($n = 30$), toxicity ($n = 22$), patient and/or physician discretion ($n = 5$), or additional adverse events ($n = 5$). See Toxicity section for further details.

3.2 Survival and Response

Fifty-three patients (82%) lived 12 months or longer. The overall median survival for the entire cohort was 19 months (range 2–91+; Table 2 and Fig. 1a). According to RECIST criteria on CT or magnetic resonance imaging (MRI), four patients achieved a complete response and 28 achieved a partial response, for a response rate of 49%. Twenty-one patients had stable disease, resulting in a disease control rate of 81% (Table 3). Survival was not influenced by either disease stage at time of diagnosis or whether patients had received prior treatment (Fig. 1b, c; Table 2). Thirteen patients (20%) had normal CA19-9 levels (≥ 36 U/mL) at the time of initial therapy, and their median survival was 30.5 months, significantly greater than the overall survival of the 52 patients who had elevated CA19-9 at start of therapy (17 months) (Fig. 1d). Of the 52

Table 1 Demographic and baseline clinical characteristics of patients who were treated

Characteristics	N = 65
Age (years)	
Median	59
Range	26–80
Sex	
Male	23
Female	42
ECOG Performance Status score ^a	
0	18
1	27
2	20
Site of primary cancer	
Head	29
Body	24
Tail	12
Prior surgery	
Yes	28
No	37
Previous chemotherapy	
Yes	28
No	37
Disease stage	
III	19
IV	46
Site of metastatic disease	
Liver	34
Lymph node	13
Lung	6
Peritoneal carcinomatosis	9
Ovary	1
Carbohydrate antigen 19-9 level	
Normal	13
Elevated	52

^aECOG = Eastern Cooperative Oncology Group

patients with elevated pretreatment CA19-9, 21 patients had 90% or greater reduction in CA19-9 levels compared with baseline. This cohort of patients had a response rate of 71%, with median survival of 28 months, versus 15 months in patients with less than 90% reduction in CA19-9 ($p = 0.004$; Fig. 1e).

Seven patients are alive and being followed off therapy at the time of analysis. Their survival ranges from 39 months to 120 months since their initial diagnosis. Two remain clinically free of disease.

3.3 Toxicity

The most frequently observed treatment-related grade 3 or 4 side effects were fatigue (21%), neuropathy (25%), stomatitis (21%), diarrhea (25%), and nausea and vomiting (9%) (Table 4).

The most common non-hematologic toxicity was neuropathy, seen in 32 patients (49%), with 16 patients (25%) experiencing grade 3 or greater. Nineteen patients discontinued therapy because of neuropathic side effects. With time, 31 of 32 patients with neuropathy improved to either grade 1 or 2.

Four patients developed a drug allergy to oxaliplatin, with three additional patients manifesting interstitial pneumonitis. All were successfully treated.

Thirteen patients (25%) developed grade 2 or greater hypertension, a known toxicity of bevacizumab. Of these, two were associated with hemolytic uremic syndrome. Both of these patients recovered.

Anemia was observed in 14 patients (22%), seven of whom had grade 3 or greater. Nine patients (14%) developed grade 3 or 4 thrombocytopenia, and 12 patients (18%) had grade 3 or greater neutropenia.

Additional events included myocardial infarction ($n = 1$), hemolytic uremic syndrome ($n = 2$), and small bowel obstruction while on therapy ($n = 1$); all of these patients recovered. One patient who developed multiple liver abscesses and sepsis secondary to cholangitis died while on therapy.

Table 2 Overall survival and survival rates among treated patients

Overall survival	All patients (N = 65)	Stage III (n = 19)	Stage IV (n = 46)
Median	19 months	19 months	19 months
Range	2–65+ months	5–42+ months	2–65+ months
Survival rate	Number	%	
6 months	59	90	
12 months	53	82	
18 months	35	54	
24 months	23	41	
36 months	12	18	

4 Discussion

Advanced, inoperable pancreatic cancer is an aggressive and rapidly fatal disease. For decades, there has been no clinically meaningful improvement in survival with therapeutic intervention for patients with metastatic disease. Standard treatments using MTD schedules have been of limited value; thus an urgent oncologic need remains unmet.

In this paper we have retrospectively analyzed the experience of 65 patients with advanced, inoperable pancreatic cancer who were treated with 5FU as a prolonged infusion in conjunction with weekly low-dose leucovorin, nab-paclitaxel,

Fig. 1 Overall survival of **a** all evaluable patients ($n = 65$), **b** stage III ($n = 19$) and stage IV ($n = 46$) patients, **c** patients who received prior therapy ($n = 28$) and those who did not ($n = 37$), **d** patients with elevated CA19-9 levels ($n = 52$) and those with normal CA19-9 ($n = 13$), and **e** patients with elevated CA19-9 with a $> 90\%$ decrease in CA19-9 ($n = 20$) and with a $< 90\%$ decrease ($n = 32$)

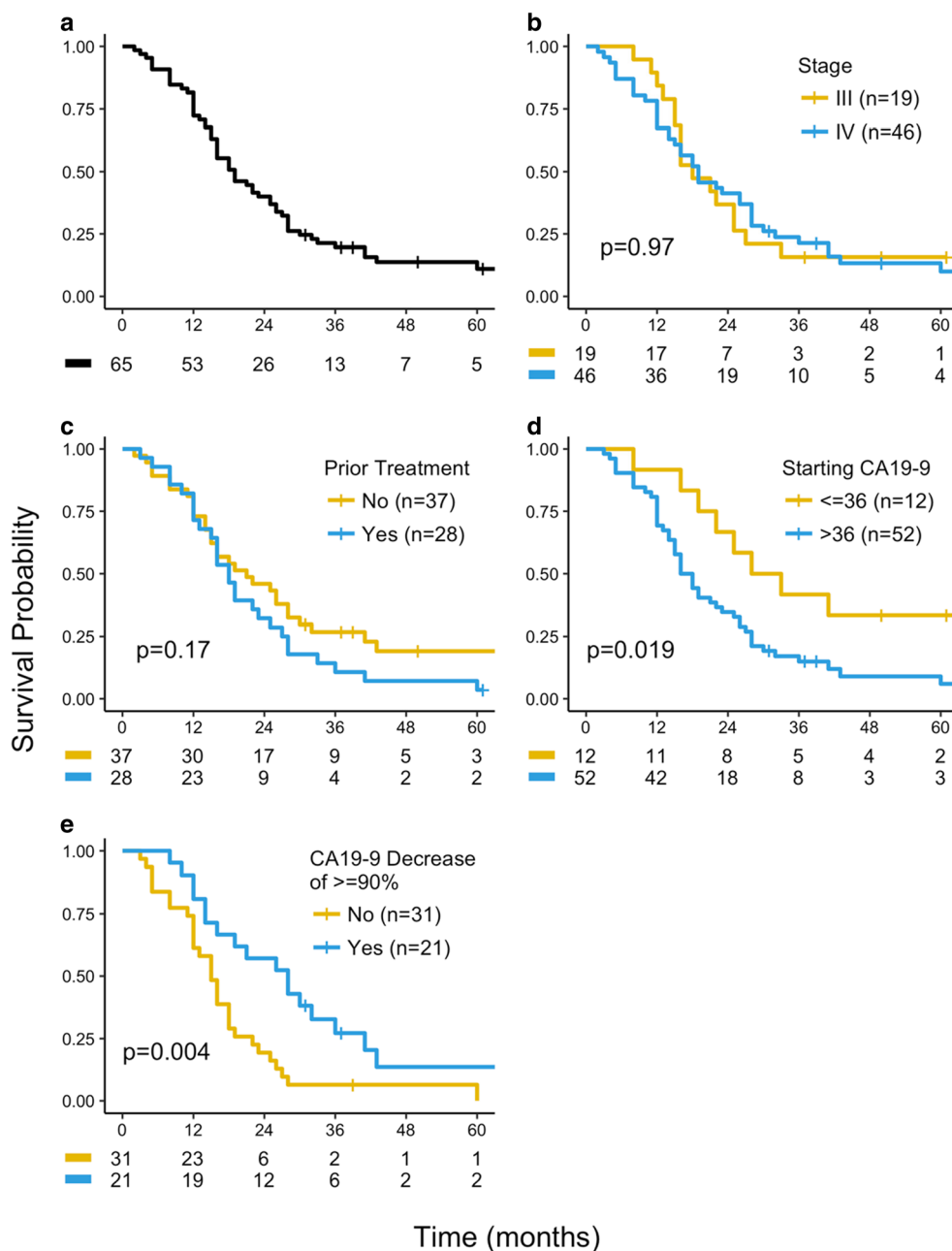


Table 3 Objective response in treated patients

Response results	Number of patients					
	Total evaluable ($N = 65$)		Stage III ($n = 19$)		Stage IV ($n = 46$)	
	Number	%	Number	%	Number	%
Complete response	4	6	2	11	2	4.3
Partial response	28	43	8	42	20	43
Stable disease	21	32	8	42	13	28.3
Progression of disease	12	18	1	5	11	24
Disease control	53	81	18	95	35	76

and oxaliplatin. Bevacizumab was added on days 1 and 15. All analyzed and reported parameters compare favorably to those observed with more conventional treatments. Patient survival at 1 year was 82%, with median overall survival of 19 months. Median survival was greater than 27 months for those patients whose serum CA19-9 level decreased by 90% or more from pretreatment values. At 24 and 36 months, survival rates were 41 and 18%, respectively, and 81% of patients had achieved effective disease control.

We observed that the survival for patients with stage III and stage IV disease were the same, 19 months. In retrospect, patients with stage III disease status at the initiation of therapy may have been inaccurately under-staged, and actually had

Table 4 Common toxicity as a result of treatment

Non-hematologic toxicity, grade ≥ 3	Number	(%)
Fatigue	14	21
Neuropathy	16	25
Stomatitis	14	21
Diarrhea	16	25
Nausea/vomiting	6	9
Hypertension (grade ≥ 2)	13	20
Renal failure	2	2
Hematologic toxicity, grade ≥ 3	Number	(%)
Anemia	7	11
Thrombocytopenia	9	14
Neutropenia	12	18

stage IV cancer. This under-staging results from the inability of current imaging techniques to detect small-volume metastasis. Previous studies utilizing gemcitabine-based therapies have reported a difference in survival between stages III and IV [5–10]. In these studies, there was limited or no therapeutic impact on survival, and hence survival differences between stages may be due to a bias in lead time to the discovery of occult metastases. In our study, median and 1-year survival rates were substantially higher than those achieved in trials of other established therapeutic regimens for pancreatic cancer. In the current work, 1-year survival was 82%, versus 45% reported for FOLFIRINOX, and median overall survival was 19 months, exceeding the 11.1 months for FOLFIRINOX [4]. With regard to the safety profile, FOLFIRINOX was associated with a 45% incidence of \geq grade 3 neutropenia, compared with 18% in our regimen [4]. We did observe less \geq grade 3 nausea and vomiting (15 vs. 9%), more \geq grade 3 diarrhea (25 vs. 13%), and a higher incidence of neuropathy (25 vs. 9%). Because of the high incidence of neutropenia associated with FOLFIRINOX, one could speculate that it would be difficult to build on this regimen. Furthermore, the median duration on therapy with FOLFIRINOX was less than 16 weeks [4], compared with 29 weeks using a metronomic schedule in the present study. Based on response, survival, toxicity, and duration of treatment, metronomic therapy exhibits a more favorable therapeutic index.

The regimen reported here also compares favorably to outcomes achieved with gemcitabine plus *nab*-paclitaxel. In the Von Hoff study, median overall survival was 8.5 months, and 1-year and 2-year survival was 35 and 9%, respectively, in the gemcitabine plus *nab*-paclitaxel group [11]. By comparison, median survival, 1-year survival, and 2-year survival reported here are 19 months, 81%, and 41%, respectively. Compared to the 49% response rate and 81% disease control rate achieved in the current study, the response and disease control rates for *nab*-paclitaxel/gemcitabine were 23 and 48%, respectively. Finally, the median duration on study for *nab*-paclitaxel and

gemcitabine was under 18 weeks, substantially less than the 29 weeks observed in the current study.

In spite of the depressing statistics resulting from mostly negative trials, oncologists continue to accept the marginal benefits of currently sanctioned therapies for pancreatic cancer. Several examples are obvious. One is the establishment of gemcitabine as the standard of care [41]. Others include the frequent use of ineffective combinations such as gemcitabine and erlotinib, gemcitabine and oxaliplatin, or gemcitabine and cisplatin [5, 10, 42, 43]. There is no conclusive evidence that these treatment protocols are better than the 5FU-based regimens which were used in the 1980s and 1990s [44].

As stated previously, metronomic dosing may inhibit tumor angiogenesis, whereas high-dose pulse therapy could potentiate it. Kamen et al. note that the idea of a log-phase dose survival curve developed by Skipper et al. was a consequence of an *in vivo* model used to study the effect of chemotherapy on cell death [45]. In these models, the dose–response effects were only valid for cells growing during the log phase. Skipper et al. clearly indicate that this model would be of limited value clinically, because growth in solid tumors is not in the log phase, and the majority of cancer cells within the tumor mass are non-proliferating during the time of drug exposure [46]. The focus has been on the “dose”, and has neglected “time”. Experimental evidence shows that endothelial cells are affected by chemotherapy at their MTD [12, 13, 47]. However, prolonged intervals between treatment allow for tumor regrowth and endothelial cell repair. The damage to the tumor endothelium is reversed by a profound rebound in circulating endothelial progenitor cells (CEPs) released from the bone marrow during drug-free intervals [48, 49]. This rebound in CEPs after MTD dosing could explain a potential mechanism for drug resistance, and thus metronomic dosing may inhibit this process [48]. Some of the most profound effects have involved various microtubule inhibitors such as vinblastine, paclitaxel, and docetaxel [50, 51]. Researchers have proposed that the pro-apoptotic properties associated with metronomic chemotherapy may be mediated by the reduction in endothelial cell specific inhibition by thrombospondin 1 (TSP1) [52, 53]. Other therapeutic agents also have angiogenic “side effects” that could work by similar mechanisms. Trastuzumab, a monoclonal antibody against ERBB2, was revealed to have antiangiogenic properties, as it inhibits VEGF expression, and can induce TSP1 in tumor cells [54–56]. On the other hand, supportive growth factors such as erythropoietin and granulocyte colony-stimulating factor (G-CSF) may actually stimulate angiogenesis, contributing to worse survival outcomes in some clinical trials [57, 58].

This study is not without limitations. Our work is a retrospective analysis of a single institution’s experience spanning almost 10 years. The lack of randomization precludes a formal comparison to other treatment modalities, as a standard treatment arm is not available. Because this is a single-institution

study, there may be additional factors unique to our patient population that could affect patient survival for which we could not control. Furthermore, there is notable heterogeneity in our study population, with a large fraction of patients having received prior therapy (chemotherapy and/or surgery) and a relatively high proportion of confirmed stage IV patients at treatment initiation.

5 Conclusion

In this report, we demonstrated the feasibility of administering multi-agent chemotherapy to an unselected patient population, giving it frequently and for prolonged periods of time, and observed that it was safe and effective. Metronomic therapy for pancreatic cancer demonstrated a good therapeutic index and non-inferiority to the current standard of care. The clinical experience reported in this retrospective analysis is a safe and effective option.

Compliance with Ethical Standards

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Conflict of Interest All authors declare that they have no financial interests related to the work described in this paper or its publication.

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